The Effect of Low-Level Laser Therapy on Bone Healing After Rapid Maxillary Expansion: A Systematic Review

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Abstract: OBJECTIVE The study aimed to systematically appraise the evidence on the effects of low level laser therapy (LLLT) on bone healing following rapid maxillary expansion (RME). METHODS Electronic search was performed in MEDLINE, Scopus, and Embase databases using appropriate Medical Subject Heading terms, with no time restriction. ClinicalTrials.gov (www.clinicaltrials.gov) was also searched using the terms "low level laser therapy" and "maxillary expansion." SELECTION CRITERIA Original research articles on human clinical trials that involved both RME and LLLT were included. Animal studies were also assessed on an exploratory basis. RESULTS The search strategy resulted in 12 publications (4 randomized controlled trials, 8 animal studies). In human studies, bone density was assessed radiographically (either two-dimensional or three-dimensional imaging). Regardless of the discrepancies in the intervention protocols, the total of the trials revealed that LLLT had stimulatory effects on bone regeneration after RME. The studies in animal models measured the formation and maturation of new bone qualitatively or quantitatively. CONCLUSIONS Despite the limited evidence, LLLT seems to be a promising intervention for stimulating immediate bone regeneration and healing after midpalatal suture expansion. Long-term, randomized clinical trials are needed to formulate safe results and establish a reliable clinical protocol, rendering the method clinically applicable.

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The effect of Low Level Laser Therapy (LLLT) on bone healing after rapid maxillary expansion: A systematic review including human and animal research

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Abstract

Purpose

The study aimed to systematically appraise the evidence on the effects of LLLT on bone healing following rapid maxillary expansion (RME).

Methods

Electronic search was performed in Medline, Scopus and Embase databases using appropriate Medical Subject Heading terms, with no time restriction. ClinicalTrials.gov (www.clinicaltrials.gov) was also searched using the terms "low level laser therapy" and "maxillary expansion".

Selection criteria

Original research papers on human clinical trials that involved both rapid maxillary expansion and low-level laser therapy were included. Animal studies were also assessed on an exploratory basis.

Results

The search strategy resulted in 12 publications (4 clinical trials, 8 animal studies). In human studies, bone density was assessed radiographically (either 2-D or 3-D imaging). Regardless of the discrepancies in the intervention protocols, the total of the clinical trials revealed that LLLT had stimulatory effects on bone regeneration after RME. The studies in animal models measured the formation and maturation of new bone qualitatively or quantitatively.

Conclusions

Despite the limited evidence, LLLT seems to be a promising intervention for stimulating immediate bone regeneration and healing after midpalatal suture expansion. Long-term, randomized clinical trials are needed to formulate safe results, and establish a reliable clinical protocol, rendering the method clinically applicable.

Introduction

Everyday clinical orthodontic practices are often called to treat crossbites, which are discrepancies in the buccolingual relationship between the upper and the lower jaws (1). Anterior and posterior crossbites may present different skeletal or local causes, the former of which constitute the most severe clinical cases. When maxilla is diagnosed as constricted and being responsible for the abnormal transverse skeletal relationship, the orthodontic treatment involves maxillary expansion in the majority of the cases. This therapeutic intervention comprises the separation and opening of the midpalatal suture through the use and activation of an intraoral fixed appliance following a personalized protocol.

Patient's age is a significant—possibly the sole—factor that determines the ultimate selection of the most suitable expansion method. Slow maxillary expansion *(SME)* is the most appropriate technique for children and young adolescents who are experiencing a mild skeletal problem, and rapid maxillary expansion *(RME)* is preferred in more severe cases. Surgically assisted maxillary expansion can overcome the drawbacks of *RME* when attempting to open a completely ossified midpalatal suture in adults (2-4).Rapid maxillary expansion is considered a safe and reliable procedure, for which modern orthodontics uses a variety of appliances, the *Hyrax* appliance being the standard tool. The only crucial limitation in obtaining a good clinical outcome is bone density, regardless of the expansion technique. Quick bone regeneration and healing of the trauma and defects that arise in the midpalatal area as a result of the opening of the suture is likely to minimize the risk of short-term relapse (4).

Low-level laser therapy *(or low-level laser treatment, LLLT)* has a wide range of clinical applications in dentistry, as well as in the field of orthodontics. As laser treatment is characterized by relative simplicity and brevity, it was applied and tested in solving issues in clinical orthodontics, which might otherwise be related with complications or delays in the orthodontic treatment itself. Such possible applications of laser therapy include the acceleration of the velocity of tooth movement, the reduction of pain during the active phase of the orthodontic treatment, the management of soft tissue problems, the production of selective force application of *Ni-Ti* arch wires, the enamel etching and the bracket bonding - debonding procedures (5).

Previous in vitro and in vivo studies have also examined the capacity of *LLLT* to accelerate bone healing after a trauma or defect (6-8). The expression profile of both angiogenic and inflammatory genes seems to be modulated by the lasers therapy. (6) Though their results are promising, the heterogeneity of the intervention and evaluation methods has prevented reliable conclusions from being drawn. *LLLT* appears to stimulate osteoblast proliferation,

collagen deposition, and early bone maturation, leading to bone neoformation (6-8). Based on the best available evidence on this field, interest has been raised in the possible application of *LLLT* on rapid maxillary expansion to facilitate faster and more predictable bone healing, which would lead to more stable long-term outcomes.

As far as the effect of low-level laser therapy on bone repair after mipalatal suture opening is concerned, the level of evidence remains confined. The lack of a systematic approach and gathering of the related data may be one possible reason for withholding the intensity of the ongoing research. Therefore, the present review was conducted with the objective of gathering and critically assessing the data which derive from studies in the field, aiming to elucidate whether the *LLLT* has ultimately positive effects on bone healing after rapid maxillary expansion.

Materials and Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) were followed for reporting of this systematic review (9,10).

Search strategy

A systematic search was conducted using the Pubmed database, the Embase and Scopus with no restriction on year of publication. In addition, the ClinicalTrials.gov registry was searched for unpublished literature. The electronic search was repeated during the first week of July 2016, so as current data to be retrieved.

The Medical Subheading terms *(MeSH terms)* related to maxillary expansion and LLLT, as well as the search strategy built for the abovementioned databases are depicted in the Appendix. Free text words, such as “orthodontics”, “rapid maxillary expansion”, “low-level laser treatment” and “LLLT” were also used during a second search in the Medline database.

Eligibility criteria and study selection

Taken the limited evidence of the effect of laser therapy on midpalatal bone healing into consideration, the authors decided to include into this review all related scientific papers that could be assessed and provide more evidence to the topic. Thus, the inclusion and the exclusion criteria were formed as presented below.

Inclusion criteria

The articles included in this study were:

1. Randomized clinical trials

2. Controlled Clinical trials, in which the intervention included surgically assisted rapid maxillary expansion

3. Original research papers on animal studies. These studies will be included on an exploratory basis and presented as secondary sources of information.

The type of the functional appliance used was not a limiting factor in the selection of a study.

The criteria for excluding articles from this review were as follows:

1. Studies irrelevant to LLLT

2. Case reports

3. Clinical trials, in which patients suffered from craniofacial deformities (e.g. cleft palate)

4. Studies that used expansion appliances in the context of distraction osteogenesis of the mandible

Data collection

The systematic search was conducted by one of the authors *(FS)* and a list including the titles of the articles gathered, was created. Per our criteria, each reviewer *(FS and AT)* examined the list independently and decided upon the articles to be included. Articles that apparently did not meet the inclusion criteria were further examined, based on their abstracts. Discrepancies between the two investigators *(FS and AT)* were settled by a thorough reading of the full-text article and discussion. The final list of the articles selected were examined further by a well-trained and experienced researcher *(ETF)* to avoid possible systematic errors. The three examiners also performed a quality assessment of the included studies, after the removal of the duplicates, and reached a consensus through discussion.

Data extraction

The data from the studies were organized into 3 tables. (Table 1-3) The first table summarized the information on the clinical trials (eg, authors, publication year, type of study, number of participants, groups, expansion and consolidation period, measure method, outcome). The second table was used to record the protocol data of lasers therapy that was applied in the clinical studies. Lastly, data on the animal studies were listed in the third table. Animal

studies were assessed on an exploratory and descriptive basis. The two investigators *(FS, AT)* collected independently the data from the related articles and any disagreements raised were arranged by the third investigator. *(ETF)*

Risk of Bias within studies

Risk of bias in individual studies was assessed according to the Cochrane Risk of Bias tool for both RCTs and CCTs (11). In particular, the following domains were considered:
1. random sequence generation, 2. allocation concealment, 3. blinding of participants and/ or personnel involved in the study, 4. blinding of assessors, 5. incomplete outcome data reporting, 6. selective reporting of outcomes, 7. other sources of bias. An overall assessment of the risk of bias was made for each included study (high, unclear, low). Trials with at least 1 item designated to be at high risk of bias were regarded as having an overall high risk of bias. Trials with unclear risk of bias for one or more key domains were considered to be at unclear risk of bias and trials with low risk of bias in all domains were rated as low risk of bias. By convention it was regarded that CCTs were to be rated as of high risk of bias for the first two domains pertaining to the risk for selection bias.

Summary Measures and Data Synthesis

Clinical heterogeneity of included studies was assessed through the examination of individual trial settings, eligibility criteria, appliances used and data collection methods. Statistical heterogeneity was to be examined through visual inspection of the confidence intervals *(CIs)* for the estimated treatment effects on forest plots. Also, a chi-square test was to be applied to assess heterogeneity; a p-value below the level of *10% ($p<0.1$)* was considered indicative of significant heterogeneity. I^2 test for homogeneity was also to be undertaken to quantify the extent of heterogeneity (12).

Only studies at unclear or low risk of bias overall were intended to be included in meta-analyses. Random effects meta-analyses were to be conducted as they were considered more appropriate to better approximate expected variations in trial settings. Treatment effects were calculated through pooled standardised mean differences (SMD) along with associated *95%.* Confidence Intervals *(95% CIs)* and Prediction Intervals where applicable (at least 3 trials needed).

Risk of bias across studies

If more than 10 studies were included in meta-analysis, publication bias was to be explored through standard funnel plots (13).

Additional Analyses

Sensitivity analyses were pre-determined to explore and isolate the effect of studies with unclear risk of bias on the overall treatment effect if both low and unclear risk of bias studies were included.

Results

A total of two hundred fifty-four scientific papers were retrieved from the electronic search we conducted. More specifically, our electronic search strategy in the *Medline* database resulted in nine papers, while two-hundred thirty-six and nine articles were gathered from *Scopus* and Embase respectively. Handsearch in *Pubmed* and *GoogleScholar* using related keywords yielded one additional scientific paper. Clinicaltrials.gov did not yield any additional article. The duplicates, which counted six, were removed. The round of screening involved the evaluation of sixteen abstracts. Among them, two studies applied low-level laser treatment in the context of distraction osteogenesis of the mandible by means of the Hyrax appliance, (14, 15), one presented a unique case (16), and one clinical trial offered insufficient data about the expansion and the laser's intervention protocol (17).

The above mentioned studies were excluded from our review.

Following the inclusion criteria that were set for the present review, 7 articles from the *Pubmed*, (18-24), 4 articles from *Scopus* (25-28), and the one additional paper (29) were finally included in our study. The number of papers that were finally included for data analysis was 12 after duplicate removal.

Our study flow diagram is depicted in *Figure 1*.

Study samples

The articles included controlled clinical trials and laboratory studies on animal models. Specifically, four reports of randomized controlled trials, involving surgically assisted maxillary expansion *(SARME)* in the 2 studies (18,19) and rapid maxillary expansion with a Hyrax expander in the remaining publications (27,28).

Laser type

As far as the clinical trials is concerned, diode laser was applied in all the four of them (18,19,27,28). The wavelength of diode laser used did not range significantly (660-830 nm), while both Cepera et al (19) and Fereira et al (27) preferred diode laser 780 nm for their intervention.

Orthodontic method and expansion period

Traditionally, orthodontists have preferred tooth-borne and tissue-tooth-borne devices, such as the Hyrax and Haas, for rapid maxillary expansion and surgically assisted rapid palatal expansion. The Hyrax expander was used in the 4 RCTs (18,19,27,28)

Cepera and co-workers noted significant disparities in the final effect on bone healing between 5 groups, which were subjected to several irradiation protocols, differing in the onset and frequency of application (19). Angeletti et al. reported a stimulatory effect of *LLLT* on bone healing in its early stages but failed to observe any differences between the irradiated and control groups after 7 months (18).

Methodology for outcome assessment

The effect of laser treatment on bone regeneration was measured using various methods among studies. In clinical trials, bone density was assessed radiographically (digital photographs, CT scan, periapical x-rays) after the intervention and compared with a control, non-irradiated group (18,19,27,28)

Data synthesis

No meta-analysis could be implemented in view of the apparent heterogeneity in individual trial settings, appliance protocols and methodology for outcome assessment followed. Consequently, publication bias detection or other secondary analyses were not performed as well.

Risk of Bias within studies

Details on the reporting of randomization and allocation concealment strategies were insufficient in all of the included studies. High risk of bias was noted for randomization in one study (27). A similar trend was detected also for items pertaining to blinding/masking of the personnel involved. In this case it was acknowledged that blinding of the investigators or the patients was not possible due to the nature of the interventions. Three studies reported

blinding of the investigator/ radiologist who was responsible for data recordings (18,27,28). Only one study (27) was rated as high with regard to risk for attrition bias as half of the participants were lost only form one of the groups. Last, selective reporting was rated as low risk of bias in all studies since sufficient details were included to allow for the assessment and pre-determination of study outcomes (18,19,27,28). However, none reported any pre-registration of a trial protocol (Figure 2).

Animal studies

According to the inclusion criteria set for the present review, 8 laboratory studies were finally included in our review, so as the findings of the clinical trials to be more clearly explained. Among them, 7 studies were performed in rats (20,22-26,29), compared with 1 in dogs (21). Bone formation was evaluated in all of these studies after the animals' death.

Laser type

The most common laser type for the *LLLT* in these studies was gallium-aluminum-arsenide (Ga-Al-As, also known as diode lasers). More specifically, 10 out of the 12 included studies (83.3%) preferred diode laser for the lasers intervention. One study used a combination of a diode laser and light-emitting diode *(LED)* phototherapy (23). Another important parameter of laser treatment is the wavelength (nm) that that laser emits. In the included animal studies, the emission of the *Ga-Al-As* lasers fluctuated from 780 nm to 830 nm (20, 24-26, 29)

In Rosa et al., the diode laser had a 780-nm wavelength, whereas the *LED* laser emitted at 850 nm (23). LED light was solely used by Ekizer et al, at 618nm(22). The photon laser, which was used only in Santiago et al., emitted from 790 to 904 nm (21).

Orthodontic method and expansion period

With regard to the devices utilized in midpalatal suture opening, helical springs (22,24,26), circular metal rings that were placed between the maxillary incisors (20,25), coil springs made of orthodontic wire (29), and orthodontic triple helicoid springs (23) were applied. In 6 studies, the expansion period was approximately 5 to 8 days when the sample constituted a single group (18,19,23,27-29)

In 4 studies, the study sample was divided into several groups, with the investigators evaluating bone formation after various periods of expansion, with or without laser irradiation

(20,23,25,26). In another study, several experimental groups were examined at various time points (29).

The time point of the onset of laser irradiation and the frequency of the irradiation protocol varied significantly between studies. Six studies applied laser irradiation directly after expansion of the midpalatal suture (20,22,25,26, 29). Altan et al. performed laser irradiation around the midpalatal suture after 5 days of midpalatal suture expansion and every other day, for a total of 4 treatment sessions (24). Aras et al. applied the laser on Day 5 postexpansion until Day 7 (26.

Methodology for outcome assessment

The studies in animal models measured the formation and maturation of new bone by immunohistochemistry qualitatively or quantitatively. Tissues from the midpalatal area of the irradiated and nonirradiated groups were sampled, stained, and analyzed with regard to bone neoformation by measuring osteoblasts and other vessels or molecular regulators of bone remodeling, such as growth factors and alkaline phosphatase. Only de Silva et al. combined immunochemistry with a pure quantitative expression analysis of genes that were related to bone repair, such as *Runx 2*, by real-time PCR (20).

Regardless of the discrepancies in evaluation methods, these studies reported stimulatory effects of *LLLT* on bone regeneration after *RME.*

As far as the intensity or the ongoing research on this topic, the vast majority of the studies, approximately 85% of them, was conducted during the period 2012-now. Apart from this, two randomized clinical trials were published in 2016, following the peak of published data, mainly from animal studies, which was noticed in 2012 and 2015. A graphical representation of the progress research and publications in the field is depicted in *Figure 3*.

Discussion

This systematic approach evaluated the effects of *LLLT* on bone regeneration in the midpalatal suture after rapid maxillary expansion with orthodontic functional appliances and surgically assisted rapid palatal expansion. We noted rising interest in the scientific community over the past 10 years, but few studies have been performed in this area—primarily in animal models. Only 4 clinical trials have determined the effects of laser treatment on bone during opening of the median palatine suture.

Regarding human studies, all reported RCTs conclude that LLLT when applied in RME cases enhances immediate bone regeneration and healing after midpalatal suture expansion, despite the differences in the application protocol, the wavelength, the irradiated points, and the energy applied. These findings were more profound on those that utilized 3-D imaging (Cone Beam Computed Tomography – CBCT) as an evaluation tool.

Laser irradiation correlated significantly with a decrease in pain after maxillary expansion (18), accelerated healing (19,22,26) and a significant rise in bone density (18,19). Animal studies conducted in this field demonstrate the influence of lasers treatment on bone repair on cellular and molecular level, although these findings must be carefully interpreted and results not directly extrapolated to human. The clinical trials included could only evaluate the final outcome of the intervention, by assessing the deposition of bone in the midpalatal area.

Histological analysis of bone tissue from the midpalatal area revealed a major increase in the numbers of osteoblasts, fibroblasts, blood vessels, and undifferentiated cells in the irradiated group. These findings demonstrate the tendency of bone tissue to repair the acute trauma that is caused by the separation of the palate. Consistent with these findings, *TGF-β,* a master regulator of osteogenesis, was up-regulated in the irradiated group (22,24)

Only da Silva et al. studied the expression profile of genes that are related to bone neoformation. *ALP*, *Runx2*, *osteocalcin*, *collagen*, and *bone sialoprotein* were overexpressed in the laser-treated group compared with the nonirradiated group (20). Other advantages of *LLLT* were highlighted, such as its easy application and clinical use, its restricted application time, and the absence of side effects (19).

With regard to laser types, the semiconductor diode gallium-aluminum-arsenide laser *(Ga-Al-As),* emitting at wavelengths of 808 to 830 nm, was the preferred treatment, for which 830 nm was the most common wavelength (20,21,25). The *"TWIN"* diode laser in Cepera et al. was also effective in accelerating bone repair (18). Similar results were obtained with the photon laser (790–904 nm) (18).

The use of a light-emitting diode photobiomodulation *(LED)* device in 2 studies also accelerated new bone regeneration (22,26). The number of osteoblasts, osteoclasts, and vessels rose in the group that was irradiated with *LED* (12). Only 1 study compared the effects of diode laser treatment and *LED* phototherapy on osseous regeneration and bone tissue maturation in the expanded midpalatal suture—hydroxyapatite *(CHA)* peak values were greater when *LED* was applied, constituting *LED* irradiation as an alternative method of *LLLT* (23).

With regard to application area of the laser treatment, most studies irradiated specific points around the midpalatal suture. Few studies proposed additional application of the laser to the region around the premaxillary sutures, located at the incisive papilla (20-22, 26) These studies failed to note significant differences between application protocols.

Some laboratory studies reported a significant outcome regarding the efficacy of laser application in new bone regeneration and its dosage. Altan et al. applied a Ga-Al-As laser at low (0.15 J), medium (0.65 J), and high doses (198 J) to the midpalatal suture after rapid maxillary expansion with a helical spring that was made from stainless steel orthodontic wire and found a significant effect on bone regeneration at 5 and 6300 J/cm2 but not 20 J/cm2 (24). Also, Saito et al. found that high doses of 6354 and 21,180 J/cm2 stimulated bone formation after rapid midpalatal suture expansion (25).

Further studies are needed to determine the appropriate dose of an *LED* laser (22,23) and soft tissue laser. Moreover, the parameters of the laser device that affect the required dosage, such as the depth of the irradiated tissue, must be evaluated (24).

Certain groups emphasized the duration of the laser application and the intervals between interventions as other important parameters that influence the clinical outcome. Bone regeneration in the histological studies that measured cell elements peaked on Day 7 (26,29). Amini et al. observed greater osseous regeneration in the third and fourth weeks after the onset of laser treatment compared with bone neoformation in the first week (29). Da Silva et al. proposed the initial application of *LLLT* after rapid maxillary expansion *(RME)* and continuous irradiation for up to at least 2 weeks. According to their findings, the peak effects of *LLLT* on cell activity occured in vivo around 2 days after the first irradiation session, but the mineralization continued to rise at Day 17 (20). Conversely, Saito et al. recommended intermittent application of the laser in the early stages of the midpalatal suture expansion, finding it to be more effective than a single dose in accelerating bone formation (25).

Concluding, LLLT is an effective and promising intervention for stimulating immediate bone regeneration and healing after midpalatal suture expansion that leads to more stable long-term clinical outcomes and less risk of relapse. The retention period might be shorter, which is a significant advantage for the therapist and the patient. As most of the existing literature shows low level of evidence, further studies, especially long-term, prospective randomized controlled clinical trials, are needed to generate safety results and render the method clinically applicable.

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INFORMATION ON THE RANDOMIZED CLINICAL TRIALS CONCERNING AUTHORS, PUBLICATION YEAR, TYPE OF STUDY, NUMBER OF PARTICIPANTS, GROUPS, EXPANSION AND CONSOLIDATION PERIOD, MEASURE METHOD, REGION EVALUATED, AND OUTCOME

Authors and publication year	***Number of participants***	***Groups***	***Expansion period***	***Consolidation period***	***Measure method***	***Region evaluated***	***Outcome***
Angeletti et al. (2010)[23]	13 Patients aged 18–33 years	Nonlased (6 patients) Laser group (7 patients)	7 Days Hyrax following SARME	4 Months	Digital periapical radiographs	Incisor region and the anterior region of the midpalatal suture	Stimulation of bone repair Relapse in the 7-month follow-up
Cepera et al. (2012)[24]	27 Patients aged 8–12 years	Nonlased (13 patients) Laser group (14 patients)	8 Days Hyrax following SARME	90 Days	Standardized occlusal radiographs	Midpalatal suture	Stimulation of bone repair
Garcia et al. (2016)[33]	39 Patients aged 6–12 years	Nonlased (19 patients) Laser group (20 patients)	Twice daily Hyrax activation until 50% transversal overcorrection	6 Months	CBCT imaging	Inferior and superior suture of the maxilla	Stimulation of bone repair
Fereira et al. (2016)[32]	14 Patients aged 8–14 years	Nonlased (4 patients) Laser group (10 patients)	Hyrax expander (twice daily activation) for 14 days approximately	4 Months	CBCT imaging	Anterior region of the maxilla	Stimulation of bone repair

CBCT, cone beam computed tomography; PA, periapical radiograph; RCT, randomized clinical trial; SARME, surgically assisted rapid maxillary expansion.

TABLE 2. ADDITIONAL DATA FOCUSING ON THE PROTOCOL OF LOW LEVEL LASER THERAPY APPLIED IN THE RANDOMIZED CONTROLLED TRIALS

Authors and publication year	*Laser type*	*Wavelength (nm)*	*Output power (mW)*	*Number of interventions*	*Dosage (J/cm^2)*	*Irradiation time*	*Method of irradiation*
Angeletti et al. (2010)[23]	Diode	830	100	8 Irradiations with 48 h interval	140 per point	84 sec per point	3 Points near MPAS
Cepera et al. (2012)[24]	Diode	780	40	Different interventions among groups	10	10 sec per point	10 Points near MPAS
Garcia et al. (2016)[33]	Diode	660	100	7 Applications	23 (Point A) 12 (Point B)	60 sec	4 Points along MPAS (points A) plus a point on either side of the suture (point B)
Fereira et al. (2016)[32]	Diode	780	70	12 Applications (twice a week for the first month, once for the second)	35	20 sec	In contact with the mucosa (incisal papilla, right and left of MPAS, posterior)

MPAS, midpalatal anterior suture.

TABLE 3. DATA ON THE ANIMAL STUDIES CONCERNING AUTHORS AND YEAR OF PUBLICATION, SPECIES OF THE ANIMALS USED, EXPERIMENTAL GROUPS, EXPANSION PERIOD, CONSOLIDATION PERIOD, MEASURE METHOD, AND OUTCOME

Authors and year of publication	*Species*	*Number of animals*	*Groups*	*Expansion period*	*Consolidation period*	*Measure method*	*Outcome*
Saito et al. (1997)[30]	Rats	76	4 Groups Nonirradiated, 1/3/7 days irradiated	7 Days	None	Histologic evaluation Fluorescent microscopy	Stimulation of bone repair
da Silva et al.[25]	Rats	30	2 Groups Nonirradiated group, Irradiated group	Immediate palatal expansion	None	Real time PCR Runx-2, osteocalcin, type-1 collagen, ALP	Stimulation of osteoblastic phenotype
Rosa et al. (2014)[28]	Rats	20	4 Groups No treatment, only expansion, expansion and LED Expansion, and LLLT	8 Days	None	Raman spectroscopy of rat's Maxilla	Increased deposition of HA
Santiago et al. (2012)[26]	Dogs	11	2 Groups Nonirradiated group, Irradiated group	7 Days	33 days	Histological evaluation, connective tissue, bone, blood vessels, cells	Stimulation of bone repair
Ekizer et al. (2013)[27]	Rats	20	2 Groups Nonirradiated group, Irradiated group	5 Days	10 days	Histological measurement of osteoclasts, osteoblasts, vessels in 1.5 mm^2 area.	Stimulation of bone repair

TABLE 3. DATA ON THE ANIMAL STUDIES CONCERNING AUTHORS AND YEAR OF PUBLICATION, SPECIES OF THE ANIMALS USED, EXPERIMENTAL GROUPS, EXPANSION PERIOD, CONSOLIDATION PERIOD, MEASURE METHOD, AND OUTCOME

Authors and year of publication	***Species***	***Number of animals***	***Groups***	***Expansion period***	***Consolidation period***	***Measure method***	***Outcome***
Altan et al. (2015)[29]	Rats	28	4 Groups: Nonirradiated, high, medium, and low dose group	5 Days	10 days	Immunostaining with anti-TGF-β	Dosage-dependant Stimulation of bone repair
Amini et al. (2015)[34]	Rats	78	4 Groups: Nonirradiated, Treated for 7, 14, and 30 days	3 Groups: 7 days 14 days 30 days	None	Histological evaluation of bone regeneration	Stimulation of bone repair, Late effects of LLLT
Aras et al. (2015)[31]	Rats	32	2 Groups Nonirradiated group, Irradiated group	7 Days	10 days	Histological measurement of the number	Stimulation of bone repair

HA, hydroxyapatite; LLLT, low level laser therapy; PCR, polymerase chain reaction.

TABLE 4. ADDITIONAL DATA FOCUSING ON THE PROTOCOL OF LOW LEVEL LASER THERAPY APPLIED IN THE ANIMAL STUDIES

Authors and year of publication	***Laser type***	***Wavelength (nm)***	***Output power (m W)***	***Number of interventions***	***Dosage (J/cm^2)***	***Irradiation time***	***Method of irradiation***
Saito et al. (1997)[30]	Diode	830	100	7-Day irradiation group	126	Group 1: 3 or 10 min/day	Around midpalatal suture
				3-Day irradiation group	420	Group 2: 7 min/day for days 0–2	
				Single irradiation group		Group 3: 21 min on day 0	
da Silva et al. (2012)[25]	Diode	830	30	Single application after expansion	160	0.42 sec	In contact with and aligned perpendicular to the palatal mucosa at the median points between the anterior edges of incisors and papilla
Rosa et al. (2014)[28]	Diode	780	70	3 Interventions on	54	257 sec	Midpalatal suture and the cortical area close to it
	LED	850	150 ± 10	day 1, 3, 5		120 sec	
Santiago et al. (2012)[26]	Photon	790–904	NR	20 Interventions with 48-h intervals	90–120	NR	4 Points bilaterally and parallel to the suture
Ekizer et al. (2013)[27]	LED	618	20	10 Daily interventions from days 0 to 10	24	20 min	Intermaxillary suture

TABLE 4. ADDITIONAL DATA FOCUSING ON THE PROTOCOL OF LOW LEVEL LASER THERAPY APPLIED IN THE ANIMAL STUDIES

Authors and year of publication	***Laser type***	***Wavelength (nm)***	***Output power (m W)***	***Number of interventions***	***Dosage (J/cm^2)***	***Irradiation time***	***Method of irradiation***
Altan et al. (2015)[29]	Diode	820	LD Group: 50 MD group: 50 HD group: 100	4 Treatment sessions	LD group: 5 MD group: 20 HD group: 6.300	LD group: 3 sec MD group: 13 sec HD group: 1.98 sec	Around midpalatal suture
Amini et al. (2015)[34]	Diode	810	NR	3 Sessions on day 7, 14, 30	4	NR	3 Points palatally, one point buccally
Aras et al. (2015)[31]	Diode	808	250	Daily between day 4–7	5	20 sec	Premaxillary regions

HD, high dosage; LD, low dosage; LED, light-emitting diode; MD, medium dosage, NR, not reported.